THE PROMISE AND CHALLENGE OF ADAPTIVE DESIGN IN ONCOLOGY TRIALS

Dr. Lyon Gleich, Vice President of the Medical Department at Medpace, discusses challenges in adaptive design in oncology trials.

Clinical oncology trials are more complex and time consuming than those in any other therapeutic area and failure rates are frustratingly high. Given the urgent need for new oncologic therapies, sponsors are eager to find more effective ways to conduct clinical research.

Incorporating adaptive design methodologies into clinical trials can reduce costs and enhance efficiency while maintaining trial integrity. They can also reduce th enumber of patients on placebo and sub-therapeutic doses. In light of this promise, regulatory bodies have created guidelines supportive of adaptive design.

Despite their potential adaptive designs are currently used in only about 20% of clinical trials. Industry sponsors cite their lack of experience with the approach and a lack of experience on the part of the contract research organizations (CROs) with whom they partner as a key reason for this low adoption rate. [1] To successfully implement an adaptive design model, sponsors must seek out research partners who have demonstrated experience in complex modeling; expertise in protocol design and statistical analysis, advanced technological capabilities and an in-depth understanding of the regulatory environment are essential.

WHAT IS ADAPTIVE DESIGN?

In its draft guidance issued in 2010, the FDA defined adaptive design as "a study that includes a prospectively planned opportunity for modifications of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study." [2]

The essence of adaptive design lies in continual learning. Traditional trial design depends on collecting data according to a rigid protocol and analyzing outcomes at the end of the trial. Under the adaptive design model, researchers rely on interim data at established points throughout the trial to inform their next steps. Building flexibility into protocol design enables researchers to make data-driven modifications during the trial resulting in faster, less expensive, more effective studies.

It is critical to note that while adaptive design is flexible, it is in no way spontaneous. Data analyses, which can be performed in a blinded or unblinded manner and can occur with or without formal hypothesis testing, are performed at predetermined points in the trial and potential adjustments based on that data are described prospectively.

SAVING LIVES, MONEY AND TIME

Clinical researchers are painfully aware that the failure rate of oncology drug testing is frustratingly high. Between 2003 and 2010, only 34% of Phase III drugs achieved statistical significance in their primary end points.[3] Those failures come at a tremendous financial cost to industry sponsors, but at a far greater cost to patients in desperate need of better treatment options.

Traditional research is rigid and, consequently, time consuming. Assumptions are made at the outset of a trial based on limited information to establish a rigid protocol. Years may pass, if endpoints such as survival and disease progression are used as endpoints, before researchers can analyze their data, at which point they may discover their preliminary assumptions were misguided.

Adaptive design enables researchers to address numerous questions simultaneously and make data-informed decisions to adjust the course of a trial. For example adaptive designs can be used to:

- Make treatment assignments based on a probabilistic formula; In adoptive randomization probability of treatment assignment changes according to the assigned treatments of patients already in the trial
- Adjust sample sizes and identify – and drop -- ineffective treatments more quickly; Research conducted by The Tufts University Center for the Study of Drug Development (CSDD) estimates that early study terminations due to futility and sample size re-estimation could save sponsor organizations between $100 million and $200 million annually in direct and indirect costs.[4]
- Establish dosing levels
- Identify biomarkers, including serum or molecular markets, which can provide critical early measures of efficacy and guide trial adaptations
- Seamlessly integrate Phase II and III trials; Rather than working sequentially to learn about a therapy in one phase and confirm its efficacy in the next, researchers can use data to adjust the protocol as they move forward, effectively merging the two phases

These types of adaptations have the potential to reduce dramatically the number of amendments researchers must make to protocols. Tufts CSDD estimates single amendment can cost an organization nearly $500,000 in direct costs and requires 60 days to implement.[5]

STUDY EXPERIENCE

Adaptive design is particularly useful in situations where patient recruitment may be slow, but efficacy and/or safety assessments can be measured quickly on an ongoing basis. The approach is ill suited to trials that require fast recruitment. The analysis of data that makes adaptive design attractive for slow recruitment can also be a deterrent in certain circumstances. Recruitment may have to be held off while an analysis of data is completed, offering little benefit compared to traditional approaches. Likewise because data is essential to determining the course of adaptive research, the approach is not appropriate for studies that take a long time to reach an observable endpoint, such as survival or disease progression.

Although many useful adaptive designs have been proposed for Phase I and Phase II studies, adaptive designs are not suited to every type of oncology trial and researchers should seek regulatory guidance before implementing adaptive designs in late-stage trials.

USE IN EARLY PHASE ONCOLOGY TRIALS

Phase I clinical trials are typically designed to establish a treatment's safety and effectiveness and the maximum-tolerated dose (MTD).

While Phase I research for many therapeutic areas is conducted in healthy participants, oncology trials are conducted with cancer patients and are used to determine the relative benefits of cytotoxic agents versus targeted agents. Determining the appropriate chemotherapy dosage levels for these patients, who are already suffering the effects of their disease, can be challenging and traditional methods for determining MTD can be slow. Adaptive design models are emerging that have the potential to identify MTD faster and to reduce the number of patients on placebo or receiving sub-therapeutic doses. Traditionally MTD is established through a 3+3 dose escalation in which successive cohorts of three participants receive a fixed dose. If the first cohort does not experience dose-limiting toxicity, a second three-person cohort is added to the trial and the dose is increased. If one person experiences dose-limiting toxicities, a third cohort is added at the same dosage level. If no patients in the third group experience dose-limiting toxicity, the dose is again escalated. If, however, a patient in the third cohort experiences dose-limiting toxicities, the MTD has been exceeded and the dosage level below is declared the MTD. Unfortunately, the 3+3 method can be time consuming.

Accelerated Dose Titration (ADT) is a more rapid approach to dose escalation that attempts to address this shortcoming. ADT can rely on single subject cohorts. Under the model fewer subjects are treated at sub-therapeutic doses and participants can receive escalated doses according to specifications established in the protocol. This allows researchers to more precisely estimate the dose-toxicity relationship and better select the dose for the next cycle for each patient. When pre-specified safety or pharmacokinetic criteria are met, the trial can be converted to a 3+3 model. Due to the extra data collected, researchers require more parameters in creating the model. While frequently applicable, it is not appropriate to use when the starting dose is thought to be close to a clinically significant potentially toxic dose.

The Continuous Reassessment Method (CRM), uses on-going risk assessment to predict doses for future cohorts based on data from earlier cohorts. The CRM approach mathematically models toxicity response as a function of dose. After each cohort, the dose-toxicity model is updated and used to select the dose for the next cohort until the MTD is identified.

LAYING THE GROUNDWORK FOR SUCCESS

Because adaptive design approaches are far more involved than standard trial designs, identifying the right research partner is essential.

Comprehensive protocol design is the cornerstone of adaptive design. To get the most out of the approach, researchers need to plan for numerous contingencies and prospectively incorporate them into the protocol.

Given the complexity of the process and the "many moving parts," assiduous up-front planning, early CRO involvement and cross functional coordination among clinical, analytical and regulatory experts is essential.

Given the sophistication of adaptive design models, superior technological and analytical capabilities are likewise essential. While implementing adaptive design involves challenges, these can be overcome through effective research partnerships and are more than offset by the potential benefits the approach offers both sponsors and patients.

REFERENCES

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